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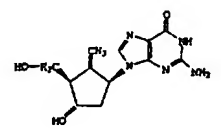
(54) Title: IMPROVED PROCESS FOR PREPARING THE ANTIVIRAL AGENT [1S-(1α, 3α, 4β)]-2-AMINO-1,9-DIHYDRO-9-[4-HYDROXY-3-(HYDROXYMETHYL)-2-METHYLENECYCLOPENTYL]-6H-PURIN-6-ONE

(57) Abstract

Improvements in the yield of the antiviral agent of formula (I) are obtained by employing Dess-Martin periodinane to convert the cyclopentol of formula (VI) to the cyclopentanone of formula (VIII) and the methylenation of this cyclopentanone to the compound of formula (XI) by use of a Nysted reagent, Tebbe reagent, or a reagent prepared from zinc powder, diiodomethane, lead powder or lead chloride, and titanium tetrachloride in a suitable solvent.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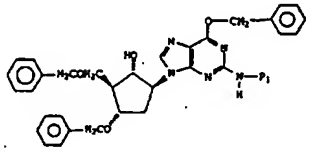
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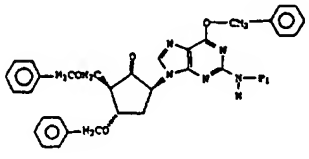
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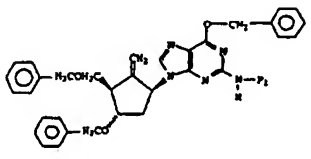
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Improved Process For Preparing The Antiviral Agent [1S-(1α,3α,4β)]-2-Amino-1,9-Dihydro-9-[4-Hydroxy-3-(Hydroxymethyl)-2-Methylene-cyclopentyl]-6H-Purin-6-One

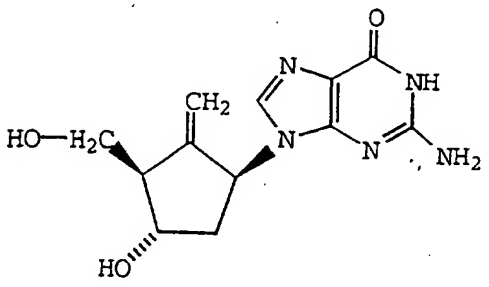
Background of the Invention

Zahler et al. in U.S. Patent 5,206,244 disclose the preparation of hydroxymethyl(methyl-enecyclopentyl)purines and pyrimidines as antiviral agents. Among the compounds disclosed is [1S-(1α,3α,4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxy methyl)-2-methylenecyclopentyl]-6H-purin-6-one.

Brief Summary Of The Invention

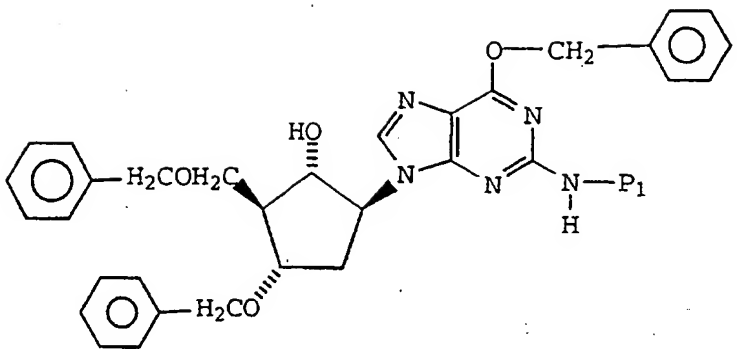
This invention is directed to improvements in several steps of the process disclosed by Zahler et al. in U.S. Patent 5,206,244 for preparing the antiviral agent of the formula

(I)



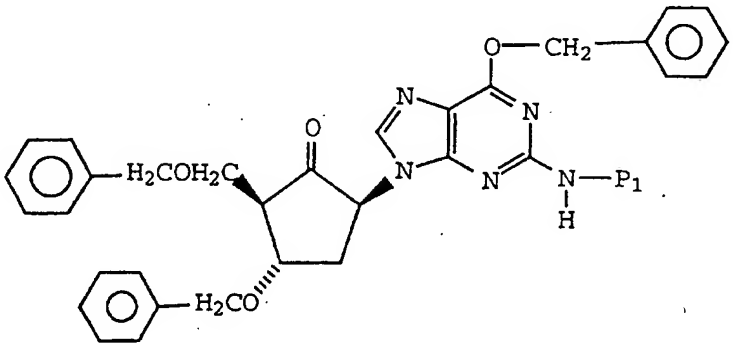
One improvement involves the step where the protected guanine substituted cyclopentanol compound of the formula

(VI)



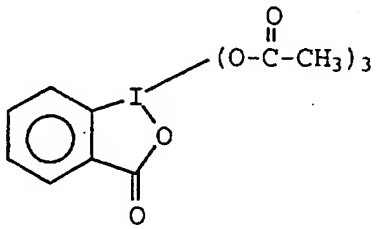
wherein P_1 is a trityl or substituted trityl protecting group such as monomethoxytrityl or 4,4'-dimethoxytrityl is oxidized to the keto compound of the formula

(VIII)



According to the improved process of this invention, the oxidation is achieved by reacting the cyclopentanol of formula VI with Dess-Martin periodinane having the formula

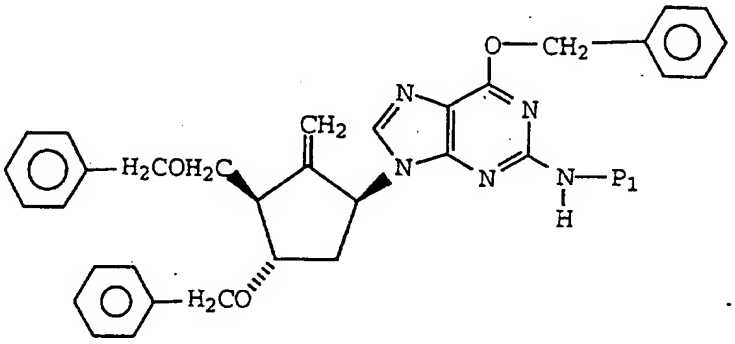
(VII)



As a result, the keto compound of formula VIII is obtained in higher yields than in the process of example 1(g) of U.S. Patent 5,206,244.

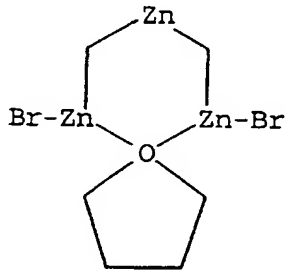
Another improvement involves the step where the keto compound of formula VIII is converted to the methylene compound of the formula

(XI)



According to the improved process of this invention, methylenation of the keto group is achieved by use of the Nysted reagent having the formula

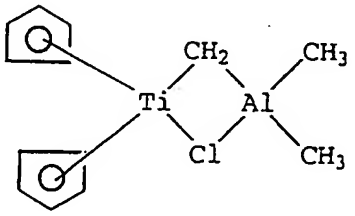
(IX)



, or

the Tebbe reagent having the formula

(X)



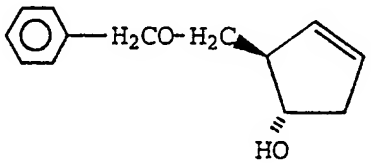
, or

a reagent prepared from zinc powder, diiodomethane, and lead powder or lead chloride in titanium tetrachloride and a suitable solvent, see Takai et al., J. Org. Chem., 1994, 59, p. 2668 - 2670 and the supplementary material. The use of the above methylenation reagents results in the preparation of compound XI in higher yields than in the process of examples 1(h) and 1(i) of U.S. Patent 5,206,244.

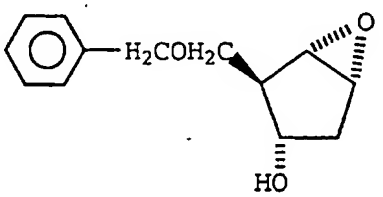
Detailed Description Of The Invention

The process improvements of this invention result in the preparation of the antiviral agent [1S-(1α,3α,4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl-2-methylenecyclopentyl]-6H-purin-6-one of formula I in improved yields. This compound possesses antiviral activity and is currently being evaluated for use in treating hepatitis B viral infections.

According to process described in Example 1 of U.S. Patent 5,206,244 the antiviral agent of formula I is prepared by treating the cyclopentenol of the formula (II)



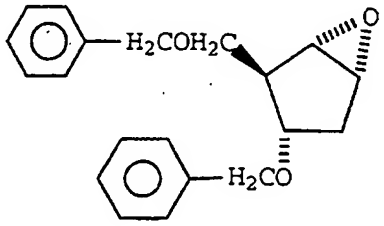
with t-butyl hydroperoxide and vanadyl acetate in dry dichloromethane to give the epoxide of the formula (III)



The epoxide of formula III can then be treated to introduce a benzyl protecting group onto the hydroxy. For

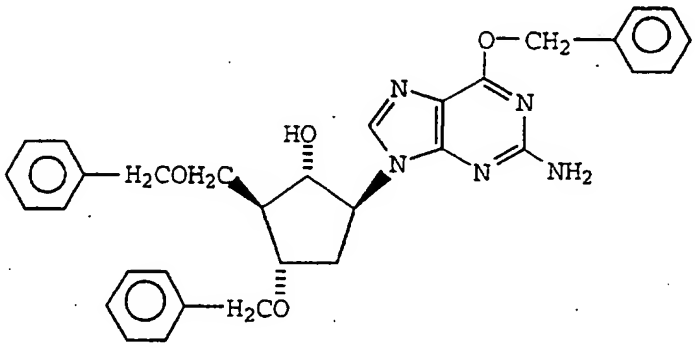
example, the epoxide of formula III in tetrahydrofuran can be added to a suspension of sodium hydride in tetrahydrofuran followed by the addition of benzyl bromide and tetrabutyl-ammonium iodide to give the epoxide of the formula

(IV)



The protected epoxide of formula IV can then be reacted with O-benzyl guanine to give the guanine substituted cyclopentanol of the formula

(V)



The amino group of the guanine substituted cyclopentanol of formula V can then be protected with trityl or substituted trityl to give the protected guanine substituted cyclopentanol of formula VI. For example, the compound of formula VI wherein P_1 is monomethoxytrityl can be obtained by treating a solution of the compound of formula V in dichloromethane with triethylamine followed by p-anisylchlorodiphenylmethane and 4-dimethylamino-pyridine.

The compound of formula VI can then be oxidized to keto compound of formula VIII. According to this invention, the yield of the keto compound of formula VIII

is increased by employing the Dess-Martin periodinane of formula VII as the oxidizing agent. Thus, the protected guanine substituted cyclopentanol of formula VI can be reacted with from about 1 to about 4 equivalents, preferably about 2 equivalents, of the Dess-Martin periodinane of formula VII at a temperature of from about -20°C to about 40°C, preferably at about room temperature, i.e. about 22°C. The reaction is performed in a suitable solvent such as dichloromethane, chloroform, 1,2-dichloroethane, other chlorinated hydrocarbons, or acetonitrile. Preferred solvents include dichloromethane, chloroform, and 1,2-dichloroethane with dichloromethane being most preferred. Optionally, water or t-butanol can be included in the reaction mixture at up to about 1 equivalent of the Dess-Martin periodinane, preferably about 1 equivalent of t-butanol is included in the reaction mixture. The reaction can be run for about 30 minutes to about 24 hours but will usually be completed in about 2 hours.

The keto compound of formula VIII can then be methylenated to the methylene compound of formula XI. According to the process of this invention, the yield of the methylene compound of formula XI is increased by the use of the Nysted reagent of formula IX, the Tebbe reagent of formula X, or the zinc reagent described by Takai et al. (J. Org. Chem., 1994, 59, p. 2668 - 2670 and supplementary material) as the methylenation reagent. The Nysted reagent of formula IX is the preferred methylenation reagent.

When the methylenation is performed with the Nysted reagent of formula IX, from about 1 to about 4 equivalents of the Nysted reagent are employed per equivalent of the keto compound of formula VIII, preferably about 1.3 equivalents of Nysted reagent. Up to about 1 equivalent of titanium tetrachloride per equivalent of the keto compound of VIII can be also included in the reaction mixture, preferably 1 equivalent of titanium tetrachloride. The keto compound of formula VIII and the Nysted reagent of

formula IX can be reacted in a suitable solvent such as tetrahydrofuran or hexamethylphosphoramide, preferably tetrahydrofuran. The reaction can be kept at a temperature of from about -78°C to about 25°C during the initial mixing and then at from about 0°C to the reflux temperature of the solvent, e.g. 66°C for tetrahydrofuran, preferably at room temperature. The reaction can be run from about one to about 72 hours but usually will be completed in about 3 hours.

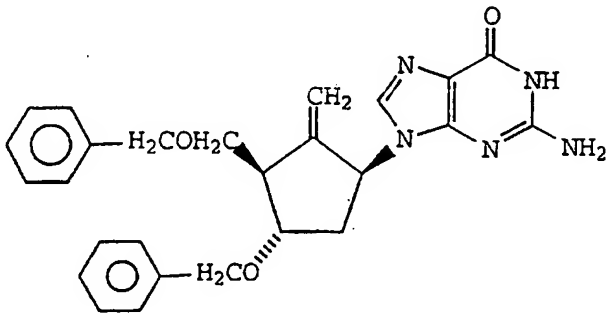
When the methylenation is performed with the Tebbe reagent of formula X, from about 1 to about 4 equivalents of the Tebbe reagent are employed per equivalent of the keto compound of formula VIII, preferably about 2 equivalents of the Tebbe reagent. The keto compound of formula VIII and the Tebbe reagent of formula X can be reacted in a suitable solvent such as tetrahydrofuran. The reaction can be performed at from about -78°C to about the reflux temperature of the solvent, preferably at about 0°C during the initial mixing and at about room temperature for the remainder of the reaction. The reaction can be run from about 15 minutes to about 24 hours but usually will be completed in about 30 minutes.

When the methylenation is performed using the zinc reagent described by Takai, et al., the reagent can be prepared by employing from about 2 to about 30 equivalents of zinc powder, from about 2 to about 20 equivalents of diiodomethane, from about 2 to about 4 equivalents of titanium tetrachloride, and from about 0.01 to 1 equivalent of lead powder or lead chloride per equivalent of the keto compound of formula VIII. The preferred reagent contains about 18 equivalents of zinc powder, about 10 equivalents of diiodomethane, about 2 equivalents of titanium tetrachloride, and about 0.09 equivalents of lead chloride per equivalent of the keto compound of formula VIII. This reaction can be performed in a suitable solvent such as tetrahydrofuran, ether or 1,2-dimethoxyethane, preferably tetrahydrofuran at a temperature of from about -78°C to

about the reflux temperature of the solvent, preferably at about room temperature. The reaction can be run from about 1 hour to about 24 hours but usually will be completed in about 3 hours.

The methylene compound of formula XI is treated to remove the O-benzyl and P_1 guanine protecting groups and give the compound of the formula

(XII)

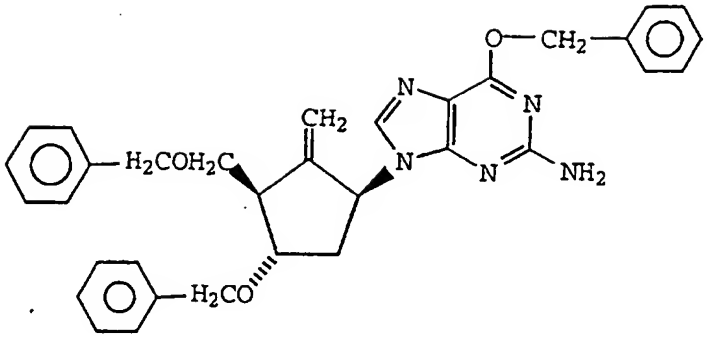


For example, a mixture of the methylene compound of formula XI, methanol and tetrahydrofuran can be treated with aqueous hydrochloric acid at a temperature of about 50°C to about 60°C for about 3 to 5 hours, the pH is adjusted to about 7, and the product is extracted with ethyl acetate to give the compound of formula XII.

The two benzyl protecting groups can be removed from the compound of formula XII to give the product of formula I in crude form. For example, a suspension of the compound of formula XII in dichloromethane at about -78°C can be treated with a solution of boron trichloride in dichloromethane to remove the benzyl protecting group.

Alternatively, the methylene compound of formula XI can be treated to remove only the P_1 protecting group and give the compound of the formula

(XIII)



For example, a mixture of the methylene compound of formula XI, methanol, and tetrahydrofuran can be treated with aqueous hydrochloric acid at room temperature for about 30 minutes to about 1 hour, the pH is adjusted to 7, and the product is extracted with ethyl acetate to give the compound of formula XIII.

The three benzyl protecting groups can then be removed from the compound of formula XIII to give the product of formula I in crude form. For example, a suspension of the compound of formula XIII in dichloromethane at about -78°C can be treated with a solution of boron trichloride in dichloromethane to remove the benzyl protecting groups.

The crude product of formula I can be purified by dissolving in methanol and concentrating *in vacuo*. The pH of the aqueous phase can be basified to a pH of about 7 by adding 1N sodium hydroxide. The neutralized aqueous solution can then be concentrated, and the precipitated solid can be filtered, washed with water, dried, and optionally purified on a reverse phase resin column to give the final product of formula I as a crystalline monohydrate.

The product of formula I and pharmaceutically acceptable salts thereof are antiviral agents that can be used to treat viral infections in mammalian species such as domesticated animals (e.g. dogs, cats, horses and the like) and humans. As set forth in U.S. Patent 5,206,244 the

product of formula I is effective against various viruses but in particular is effective against hepatitis B virus.

The product of formula I may be administered parenterally (for example, by intravenous, intraperitoneal, or intramuscular injection) orally, or topically from conventional pharmaceutical formulations containing a sufficient amount of the product of formula I or a pharmaceutically acceptable salt thereof to treat the infection. The dosage will, of course, depend upon the severity of the infection, but will likely be in the range of about 1.0 to 50 mg/kg of body weight. The desired dose may be administered from one to several times daily at appropriate intervals.

The following examples are illustrative of the invention.

Example 1

[1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, monohydrate

a) (1S-trans)-2-[(Phenylmethoxy)methyl]-3-cyclopenten-1-ol

A solution of 1M borane-tetrahydrofuran complex (1600 ml, 1.6 mole) was cooled to 0°C under an argon atmosphere and with stirring one equivalent of (1R)-(+)-α-pinene 98% (91% e.e.) (240 g, 1.6 mole) was added over 15 minutes. The mixture was stored at 5°C (no stirring) for 12 hours. A second one equivalent of pinene (240 g, 1.6 mole) was added and the mixture was again stored at 5°C (no stirring). After approximately 30 minutes, colorless crystals began to form. The mixture was stored for another 12 hours at 5°C and then the supernatant was removed by cannula and dry nitrogen was blown through the flask. The pinene-borane complex was dried under vacuum yielding about 300 g (71%) of large colorless crystals (Brown et al., J.O.C., vol. 49, p. 945 - 947, 1984).

To a solution of 92% benzyl chloromethyl ether (153 g, 0.9 mole) in 325 ml of anhydrous tetrahydrofuran at -78°C was added a 2 M solution of sodium cyclopentadienylide (450 ml, 0.9 mole) in tetrahydrofuran keeping the internal temperature between -65°C and -78°C. The reaction was stirred at -78°C for 1 hour and was then added to a suspension of the borane-pinene complex (300 g, 1.04 mole) in 900 ml of anhydrous tetrahydrofuran at -78°C, which had been stirred for 3 hours under an argon atmosphere to break up the large crystals, keeping the temperature between -60°C and -78°C. The reaction was stirred for 7 hours at -78°C and then overnight (14 hours) at -20°C. The reaction was warmed to -10°C and with rapid

stirring and 270 ml of 3 N sodium hydroxide was added keeping the internal temperature below 0°C. This was followed with the careful addition of 135 ml of 30% hydrogen peroxide keeping the internal temperature below +12°C. The reaction mixture was stirred for 1 hour at 0° to +10°C. The excess hydrogen peroxide was destroyed by adding 9 g of sodium bisulfite to the reaction mixture and stirring for 30 minutes (check for peroxide with starch iodide paper and add more bisulfite if necessary). The addition of 30 g of sodium chloride and 700 ml of ether effected separation of the organic layer. The aqueous layer was extracted with additional ether (2 x 500 ml). The combined ether extract was washed with brine and dried over magnesium sulfate. Evaporation of the solvents yielded 510 g of crude product as a yellow oil. A 5 g aliquot of the crude reaction mixture was purified on a Merck EM silica column (20:1) eluting with hexane, 5% ethyl acetate/hexane, 10% ethyl acetate/hexane and 15% ethyl acetate/hexane yielding 1.35 grams (75%) of pure product as a colorless oil, [ee = 96.9%].

The crude reaction mixture was dissolved in 1500 ml of hexane and extracted 4 times with 500 ml of 1 M silver nitrate containing 250 ml of methanol. Saturated brine was added to the aqueous solution containing the silver complex. The precipitated silver chloride was filtered and the aqueous layer was extracted with ether (3 x 500 ml). The silver chloride cake was stirred with ether yielding an additional quantity of product. The combined ether extract was dried over magnesium sulfate. Concentration of the ether extract yielded 118 grams (65%) of the desired alcohol as a yellow oil. $[\alpha]_D^{22}$ = + 71° (c = 1, chloroform).

b) [1S-(1α,2α,3β,5α)]-2-[(Phenylmethoxy)-methyl]-6-oxabicyclo[3.1.0]hexan-3-ol

To a solution of the product from part (a) (31.11 g of 76% pure by weight; 23.65 g, 115.93 mmol; contains 24% by weight of benzyl alcohol) in dry dichloromethane (70 mL) was added vanadyl acetate (0.307 g, 1.159 mmol) and the resulting light green solution was placed in a water bath at room temperature. To the solution was added a 3M solution of t-butyl hydroperoxide in isooctane (81.15 mL, 243.46 mmol) dropwise via addition funnel under argon at such a rate to keep the temperature of the reaction mixture under 20°C. Addition was complete in about 30 minutes. The mixture was stirred at room temperature under argon for 17 hours after which time no starting material remained. The mixture was placed in an ice-water bath and 120 mL of saturated aqueous sodium sulfite was added dropwise keeping the temperature below 20°C. After the addition was complete, the mixture was stirred at room temperature for 1.5 hours. Starch/iodine paper test showed no peroxide presence. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was back-extracted with ethyl acetate (2x) and combined organics (400 mL) were washed with brine, dried (magnesium sulfate) and concentrated to afford the title product (34.34 g) as a light-yellow oil. The product still contains benzyl alcohol that was present in the starting material.

c) [1S-(1α,2α,3β,5α)]-3-(Phenylmethoxy)-2-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]-hexane

60% Sodium hydride dispersion (9.232 g, 230.81 mmol of sodium hydride) was washed with pentane (3x) and the solid was suspended in 300 mL of dry tetrahydrofuran. To the suspension was added dropwise via addition funnel, a

solution of the product from part (b) (34.34 g crude; contains about 77.67 mmol of benzyl alcohol and about 16.23 mmol of t-butyl alcohol by proton NMR) in 200 mL of dry tetrahydrofuran at room temperature. Some frothing was observed initially. The addition was complete over 1 hour and the resulting dark-brown suspension was stirred at room temperature under argon for 2 hours. To the mixture was then added benzyl bromide (26.2 mL, 220.32 mmol) via syringe over 5 minutess followed by tetrabutyl ammonium iodide (0.775 g, 2.098 mmol). After 15 minutes of stirring at room temperature, some frothing was observed and the temperature of the mixture rose to 45°C. The mixture was cooled in an ice-bath and allowed to warm back to room temperature and stirred for 2.5 hours after which time no starting material remained. The mixture was cooled in an ice-bath and 1M aqueous ammonium chloride (125 mL) was added dropwise over 10 minutes. The mixture was stirred vigourously for 5 minutes at room temperature and the layers separated. The aqueous phase was extracted with ethyl acetate (1x) followed by extraction with dichloromethane (1x). The combined organics were dried (magnesium sulfate) and concentrated to obtain the crude material (55 g) as a dark-brown oil. The crude product was purified on silica gel (800 g cartridge) in a radially pressurized module (Biotage Corp.) eluting with hexane (3 L), 10% ethyl acetate-hexane (3 L) and 25% ethyl acetate-hexane (4 L). The product eluted with 25% ethyl acetate-hexane. Fractions containing product were combined and concentrated to afford pure title product (29.92 g, 83% over two steps) as a light yellow oil.

d) [1S-(1α,2β,3α,5β)]-5-[2-Amino-6-(phenylmethoxy)-9H-purin-9-yl]-3-(phenylmethoxy)-2-[(phenylmethoxy)methyl]cyclopentanol

To a solution of O-benzyl guanine (46.489 g, 192.9 mmol; dried at 50°C overnight in a vacuum oven) in dry

dimethylformamide (250 mL) was added lithium hydride (0.772 g, 96.45 mmol) as a solid (some foaming was observed). After stirring the mixture at room temperature for 10 minutes, the mixture was heated at 60°C for 15 minutess followed by addition of a solution of the product from part (c) (29.9 g, 96.45 mmol) in dry dimethylformamide (150 mL) via cannula. The resulting dark-brown solution was stirred at 60°C for 15 minutes and the temperature of the mixture was raised to 125°C over 45 minutes. After 2 hours at 125°C, no starting material remained. The mixture was cooled to room temperature and glacial acetic acid (5.52 mL, 96.45 mmol) was added and mixture was stirred for 10 minutes at room temperature. The mixture was poured into 1200 mL of distilled water and 600 mL of ethyl acetate was added. The two layers were separated (excess unreacted O-benzyl guanine remains suspended as a solid in organic layer) and the aqueous phase was extracted with ethyl acetate (3x500 mL). The combined organic phases were filtered through Celite, the Celite pad was washed with ethyl acetate and the combined filtrate (3 L) was washed with water (3x500 mL), brine (1x), dried (magnesium sulfate) and concentrated to obtain the crude material (69.1 g). The crude still contained some O-benzyl guanine which was removed by filtering a suspension of crude in dichloromethane through a silica gel pad eluting with 5% methanol-dichloromethane. The filtrate was concentrated to obtain 51.3 g of crude material which was flash chromatographed on silica gel (800 g cartridge) in a radially pressurized module (Biotage Corp.) eluting with dichloromethane (2 L), 1% methanol-dichloromethane (2 L), 2% methanol-dichloromethane (3 L), 2.5% methanol-dichloromethane (2 L) and 3.5% methanol-dichloromethane (2 L). Most of the product eluted with 2.5% methanol-dichloromethane and was collected in two batches, 10.34 g (70% purity) and 23.65 g (80% purity). The 80% pure material was combined with product of similar quality obtained from a small-scale reaction to afford 26.9 g of

80% pure material which was again flash chromatographed on silica gel (800 g cartridge) in a radially pressurized module (Biotage Corp.) eluting with dichloromethane (2 L), 1% methanol-dichloromethane (2 L), 2% methanol-dichloromethane (2 L), 2.5% methanol-dichloromethane (3 L) and 3% methanol-dichloromethane (2 L). Fractions containing product of greater than 90% purity were combined and concentrated to afford title product (18.86 g, 92% pure). Yield of the reaction was calculated to be 51% based on total amount of title product after first chromatography.

e) [1S-(1α,2β,3α,5β)]-5-[2-[[(4-Methoxyphenyl)-diphenylmethyl]amino]-6-(phenylmethoxy)-9H-purin-yl]-3-(phenylmethoxy)-2-[(phenyl-methoxy)methyl]cyclopentanol

To a solution of the product from part (d) (18.8 g, 34.12 mmol) in 250 mL of dry dichloromethane was added triethylamine (8.08 mL, 58 mmol) followed by monomethoxy trityl chloride (11.59 g, 37.53 mmol) and 4-dimethylaminopyridine (0.208 g, 1.706 mmol). The resulting yellow solution was stirred under argon at room temperature for 27 hours after which time TLC indicated only partial conversion to product. An additional amount of monoethoxy trityl chloride (0.55 equiv), triethylamine (0.85 equiv) and 4-dimethylaminopyridine (0.025 equiv) were added and mixture stirred for an additional 48 hours but no progress in reaction was observed. At this point, the mixture was concentrated *in vacuo* and taken up in 25 mL of dry dichloromethane and the above quantities of reactants added again (the monomethoxy trityl chloride was added from a fresh, previously unopened bottle). Some progress in the reaction was observed and additional amounts of the reactants were added (3x) every 1.5 hours until no starting material was detected by TLC. The mixture was diluted with ethyl acetate (1 L) and washed with 5% aqueous sodium

bicarbonate (2x100 mL), water (2x100 mL), brine, dried (magnesium sulfate) and concentrated to afford the crude product.

The crude residue was flash chromatographed the first time on silica gel (800 g cartridge) in a radially pressurized module (Biotage Corp.) eluting with 0.5% triethylamine-chloroform (2L), 1% triethylamine-chloroform (2L), 1.5% ethanol-chloroform (3L), 1.5% ethanol-chloroform (3L), and 2% ethanol-chloroform (1L). Most of the product eluted with 1% - 1.5% ethanol-chloroform but separation from excess monomethoxy trityl chloride was not achieved and about 5% of product was converted to the starting material from part (d) under the column conditions. Two batches of material were collected; 22.42 g of monomethoxy trityl chloride contaminated product and 8.49 g of product containing 10% of the starting material of part (d). The larger batch was flash chromatographed a second time using the above conditions except that the silica gel was flushed with 0.5% triethylamine-chloroform before loading, the compound solvents used for eluting contained 0.5% triethylamine. However, decomposition to the starting material from part (d) was again observed and two batches were collected; 18.49 g of monomethoxy trityl chloride contaminated product and 3.00 g of 50% pure product contaminated with the starting material from part (d). An ethyl acetate-hexane system was then used for the chromatography to eliminate usage of a solvent such as ethanol. 18.49 g of material contaminated with monomethoxy trityl chloride was eluted with 50% ethyl acetate-hexane (2L with 0.5% triethylamine), 60% ethyl acetate-hexane (2L with 0.5% triethylamine), 75% ethyl acetate-hexane (2L with 0.5% triethylamine), 90% ethyl acetate-hexane (2L with 0.5% triethylamine), and 100% ethyl acetate (4L with 0.5% triethylamine). Product eluted with 90% ethyl acetate-hexane and fractions containing pure product were concentrated to give 13.67g of pure titled product. A fourth chromatogaphy on silica gel using the ethyl

acetate-hexane system described above was carried out on 11.49 g of impure material to give another batch of pure title product (9.48g). Total amount of pure title product after all chromatography was 23.15 g (82% yield).

f) [2R-(2α,3β,5α)]-5-[2-[[(4-Methoxyphenyl)-diphenylmethyl]amino]-6-(phenylmethoxy)-9-purine-9-yl]-3-(phenylmethoxy)-2-[(phenyl-methoxy)methyl]-1-cyclopentanone

To a slurry of Dess-Martin periodinane (5.814 g, 13.71 mmol) in dry dichloromethane (150 mL) was added t-butanol (1.383 mL, 15.077 mmol) and after a stirring under argon for 10 minutes at room temperature, a solution of the product from part (e) (9.4 g, 11.422 mmol) in dry dichloromethane (100 mL) was added via cannula. The slightly yellow mixture was stirred under argon at room temperature for 30 minutes after which time all starting material had been consumed. The mixture was diluted with ethyl acetate (1 L) and stirred vigorously with 1.5:1:1 10% aqueous sodium sulfite-saturated aqueous sodium bicarbonate-brine (280 mL) for a period of 1 hour. The phases were separated in a separatory funnel and aqueous phase back-extracted with ethyl acetate (1x100 mL). The combined organics were washed with brine, dried (magnesium sulfate) and concentrated to afford crude title product (9.8 g, 100% crude yield containing a small amount of impurity) as a light yellow solid. Conversion of another batch of the product from part (e) (13.67 g, 16.525 mmol) as described above afforded a second batch of title product (13.6 g containing a small amount of impurity).

g) [1S-(1α,3α,4β)]-N-[(4-Methoxyphenyl)-diphenylmethyl]-6-(phenylmethoxy)-9-[2-methylene-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-9H-purin-2-amine

To a suspension of activated zinc (-325 mesh, 19.45 g, 297.45 mmol) and lead chloride (0.414 g, 1.487 mmol) in dry tetrahydrofuran (300 mL) was added methylene iodide (13.31 mL, 165.25 mmol) under argon at room temperature. No change in temperature was observed during the addition of methylene iodide but after 10 minutes of stirring, the temperature had increased to 30°C at which point the temperature jumped to 65°C and the mixture started boiling. The mixture was cooled in an ice-bath until the temperature dropped and the resulting black suspension was stirred at room temperature for 45 minutes. To the stirred suspension cooled to 0°C was then added 1M titanium tetrachloride in dichloromethane (33.05 mL) slowly via syringe over 15 minutes maintaining the temperature of reaction mixture at 5° to 10°C. The ice-bath was removed and the temperature allowed to rise to room temperature over 45 minutes and stirred for 45 minutes more. To the resulting dark-brown suspension was added a solution of the product from part (f) (crude 13.6 g, 16.525 mmol) in dry tetrahydrofuran (100 mL) via cannula. The resulting black mixture was stirred under argon at room temperature over 3 hours and slowly poured into a suspension of dichloromethane (200 mL) and saturated aqueous sodium bicarbonate (400 mL). The resulting suspension was stirred vigorously and additional saturated aqueous sodium bicarbonate was added (400 mL) as needed to keep the pH basic. After stirring for 1 hour, the suspension was filtered through Celite and the Celite pad washed with ethyl acetate (4x200 mL). The two phases in the filtrate were separated and organic again stirred for 30 minutes with 250 mL of saturated aqueous sodium bicarbonate (as the pH had dropped below 7.0 at this

point). After this time, the pH of the organic phase remained at 8.0 and the phases separated. The aqueous phase was back-extracted with ethyl acetate and the combined organics were washed with brine, dried (magnesium sulfate) and concentrated to obtain 13.4 g of the crude residue.

h) [1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[2-methylene-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-6H-purin-6-one

To a solution of the product from part (g) (8.0 g, 9.768 mmol) in 1:1 tetrahydrofuran-methanol (200 mL) was added 2N aqueous hydrochloric (48.84 mL) and solution was stirred at 60°C for 4.5 hours after which time no starting material or intermediate tribenzyl compound remained. The mixture was cooled to room temperature and diluted with water (100 mL) and ethyl acetate (600 mL). The two phases were stirred vigorously and pH of the mixture adjusted to 7.0 by adding 1N sodium hydroxide. A white solid which had precipitated at this point stayed suspended in the organic phase. The two phases were separated and the aqueous phase was back-extracted with ethyl acetate and the combined organics with suspended solid were washed with brine and dried with sodium sulfate. The organic phase and suspended solid were decanted off and the suspension concentrated *in vacuo*. The product obtained was washed with cold ethyl acetate and dried to afford 4.23 g (92%) of title product as a white solid.

A second batch of product from part (g) was coverted as described above to afford 1.7 g (94%) of the title produt which was combined with the first batch and triturated twice with ethyl acetate. The combined material was then dissolved in a mixture of dichloromethane - methanol-chloroform-ethanol (500 mL), filtered to remove any insoluble material and concentrated to afford 5.75 g of pure title product as a white solid.

i) [1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one, monohydrate

To a suspension of the product from part (h) (4.3 g, 9.41 mmol) in dry dicloromethane (500 mL) cooled to -78°C was added a solution of 1M boron trichloride in dichloromethane (56.46 mL) via syringe over a period of 20 minutes. The resulting yellow turbid mixture was stirred at -78°C under argon for 1 hour and then warmed to -20°C and stirred for 15 minutes after which time no starting material remained. After a total time of 45 minutes at -20°C, the mixture was cooled back to -78°C and methanol was added slowly (300 mL). The resulting clear solution was warmed to room temperature and concentrated *in vacuo*. Additional methanol (500 mL) was added and concentrated repeating the same process once more to obtain the crude residue. This crude was combined from the crude obtained from treating an additional amount of the product from part (h) (1.372 g, 3 mmol) as described above and the combined material was taken up in water (800 mL) and extracted with ether (2x100 mL). The aqueous phase was separated and its pH adjusted from 1.95 to 7.0 with the addition of 1N sodium hydroxide. The neutralized aqueous solution was concentrated on the rotovap to a volume of 100 mL and the precipitated solid was filtered, washed with cold water and dried to obtain 3.12 g of the product. The product was further purified on CHP-20 resin column eluting with water (600 mL), 5% acetonitrile-water (800 mL), 7.5% acetonitrile-water (300 mL), 10% acetonitrile-water (600 mL), 15% acetonitrile-water (300 mL) and 20% acetonitrile-water (300 mL). Product started eluting with 5% acetonitrile-water but trailed until the end of elution. Fractions were checked by analytical HPLC and all pure fractions were combined and concentrated to afford 1.9 g of the title compound as a white, crystalline solid; m.p. 234

- 236°C (dec.) for the bulk sample and 255°C (dec.) for an analytical sample recrystallized from water.
TLC: R_f = 0.31, silica gel; 6:3:1 dichloromethane: methanol:ammonium hydroxide; UV detection
HPLC: Purity >99.8% YMC S-3 120Å ODS column, 6 x 150 mm; 100% A Isocratic (A = 90% water/methanol + 0.2% phosphoric acid); 215 nm. Retention time = 6.58 minutes.
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (br s, 1H) 7.69 (s, 1H) 6.41 (br s, 2H) 5.36 (m, 1H) 5.1 (m, 1H) 4.89 (s, 1H) 4.83 (m, 1H) 4.58 (m, 1H) 4.22 (m, 1H) 3.55 (m, 2H) 2.52 (m, 1H) 2.21 (m, 1H) 2.04 (m, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 153.4, 151.4, 151.2, 135.9, 116.2, 109.2, 70.3, 62.9, 55.0, 54.0.
Mass Spec (ESI) $(M+H)^+$ = 278; $(M-H)^-$ = 276.
IR (KBr) : 3447, 3183, 2710, 1724, 1632, 1601, 1541, 1487, 1400, 1325, 1167, 1063, 1017 cm^{-1}.
$[\alpha]_D$ = +33.2° (c = 0.30, H_2O).
Analysis calc. for $C_{12}H_{15}N_5O_3 \cdot H_2O$:
Calculated: C, 48.81; H, 5.80; N, 23.72;
Found: C, 48.81; H, 5.70; N, 23.86.

Example 2

[1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one, monohydrate

The product of Example 1 was also prepared as described below.

a) [1S-(1α,3α,4β)]-N-[(4-Methoxyphenyl)diphenylmethyl]-6-(phenylmethoxy)-9-[2-methylene-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-9H-purin-2-amine

To a suspension of Nysted reagent (20% by weight in tetrahydrofuran, 70g, 30.67 mmole) in dry tetrahydrofuran (40 ml) at -78°C under argon was slowly added a solution of [2R-(2α,3β,5α)]-5-[2- [[(4-methoxyphenyl)diphenyl-methyl]amino]-6- (phenylmethoxy)-9-purin-9-yl]-3-(phenylmethoxy)- 2-[(phenylmethoxy)methyl]-1-cyclopentanone (20 g, 24.33 mmole) [prepared as described in Example 1(a) thorugh (f)] in dry dichloromethane (40 ml) followed by a solution of titanium(IV) chloride (1.0M in dichloromethane, 24.4ml, 24.4mmole). The temperature of the mixture was not allowed to raise over -60°C during the addition. After the addition was complete, the mixture was stirred at -78°C for 15 minutes and then gradually warmed up to room temperature. After 3 hours stirring, the black solution was poured into a saturated sodium bicarbonte solution (1.0L), stirred for 30 minutes and filtered through a pad of Celite to remove the inorganic materials. The filtrate was diluted with dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x600ml). The dichloromethane extracts were combined, washed with brine, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give 21g of crude title product with consistent NMR spectra.

This reaction was repeated twice using 70 g of cyclopentanone starting material each time and afforded a total of an additional 144 g of title product. This was used in the next step without purification.

b) [1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[2-methylene-3-(phenylmethoxy)-4-[(phenyl-methoxy)methyl]cyclopentyl]-6H-purin-6-one

A solution of the product from part (a) (10g, 12.20 mmole) in methanol (130 ml) and tetrahydrofuran (130 ml) was treated with 2N hydrochloric acid (61 ml). The solution was heated at 60°C for 4.0 hours. HPLC indicated the reaction was complete. The resulting solution was

cooled to room temperature and diluted with ethyl acetate (500 ml) and water (300 ml). The pH of the solution was then adjusted to 7 with 2N sodium hydroxide. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 300 ml). The ethyl acetate extracts were combined, washed with brine, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give a gum. This was triturated with ethyl acetate to give 3.7 g of clean title product as a solid with consistent NMR spectra.

This reaction was repeated using 155 g of starting material to give an additional 52 g of title product.

c) [1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)2-methylene-cyclopentyl]-6H-purin-6-one,monohydrate

A suspension of the product from part (b) (52 g, 109.8 mmol) in dry dichloromethane (1750 ml) under argon was cooled to -78°C. A solution of boron trichloride (1.0M in dicloromethane, 660 ml, 660 mmole) was added in a period of 30 minutes. The temperature of the mixture was not allowed to raise over -60°C during the addition. After the addition was complete, the mixture was stirred at -78°C for 30 minutes and gradually warmed up to -20°C. After 30 minutes at -20°C, TLC (silica gel, 6: 3: 1 dichloromethane:methanol:ammonium hydroxide) indicated there was no starting materials. The solution was cooled to -78°C and methanol (2.0 L) was slowly added. The resulting clear solution was warmed up to room temperature and concentrated *in_vacuo*. Additional methanol (2.0 L) was added and concentrated. The residue was diluted with water (500ml) and washed with ethyl ether (2x300ml) and ethyl ether-ethyl acetate (1:1, 2x300ml). The pH of the aqueous slurry was then adjusted to 7 with 2N sodium hydoxide. The resulting slurry was heated up until it became a homogeneous solution. Charcoal was added to remove color and filtered. The filtrate was concentrated *in vacuo* to

500ml. The solid was filtered, washed with water (2x100ml), ethyl ether (2x100ml), ethyl ether-ethyl acetate (1:1, 2x100ml) and acetonitrile (300ml) and dried over phosphorus pentoxide in a high vacuum for 18 hours to give 19.6g of title product; m.p. 234 - 236°C (dec).

TLC: Rf =0.31; Silica gel;
Dichloromethane:methanol:ammonium hydroxide (6:3:1), UV.
Enantiomeric purity (ee): >98% (Estimated, other isomer could not be found).

HPLC: (Shimadzu HPLC)
YMC S-3 ODS (C-18) 6.0 x 150 mm, gradient 30 min. from 0% B to 100% B (A = 90% H_2O/MeOH + 0.2% H_3PO_4; B = 90% MeOH/H_2O + 0.2% H_3PO_4); flow rate at 1.5 mL/min., UV 220, t_R = 5.78 min., (99.3%).

^1H NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 7.70 (s, 1H), 6.43 (s, 2H), 5.36 (m, 1H), 5.12 (s, 1H), 4.88 (broad, 1H), 4.60 (s, 1H), 4.22 (s, 1H), 3.54 (m, 2H), 2.52 (m, 2H), 2.22 (m, 1H), 2.04 (m, 1H)ppm

^{13}C NMR (400 MHz, DMSO-d_6): δ 156.8, 153.6, 151.5, 151.2, 136.0, 116.0, 109.4, 70.4, 63.0, 55.2, 54.1ppm.
MS: mw = 277, $(M-H)^-$ = 276.
$[\alpha]_D$ = +35° (c = 0.38, water).

Analysis calc'd for $C_{12}H_{15}N_5O_3 \cdot 1.28H_2O$:
Calculated C, 47.99; H, 5.89; N, 23.32;
Found: C, 47.94; H, 5.66; N, 23.13.

Example 3

[1S-(1α,3α,4β)]-N-[(4-Methoxyphenyl)-diphenylmethyl]-6-(phenylmethoxy)-9-[2-methylene-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-9H-purin-2-amine

The conversion of the ketone of Example 1(f) to the methylene product of Example 1(g) and 2(a) was also performed as described below.

Nitrogen gas was bubbled with stirring through freshly distilled tetrahydrofuran for a period of one hour. To 2 ml of degassed tetrahydrofuran was added [2R-(2α,3β,5α)]-5-[2-[[(4-methoxyphenyl)diphenylmethyl]-amino]-6-phenylmethoxy-9-purin-9-yl]-3-(phenylmethoxy)-2-[(phenylmethoxy)methyl]-1-cyclopentanone (0.821 g, 1 mmol) [prepared as described in Example 1(a) through (f)] and the resulting solution was added 2 ml of 0.5 M solution of Tebbe reagent in toluene (Aldrich) via syringe. The resulting dark-red mixture was warmed to room temperature and stirred under argon for 30 minutes after which time no starting material remained. The mixture was diluted with ethyl ether (20 ml) and 0.1N sodium hydroxide was added dropwise until evolution of gas had ceased. Anhydrous magnesium sulfate was added, stirred, and the suspension was filtered through Celite®. The Celite® pad was washed with ethyl acetate (4 x 10 ml) and the combined filtrate was concentrated to yield the crude product as a dark-red solid. The crude product was purified by flash chromatography on silica gel eluting with a stepwise gradient of 0% to 40% ethyl acetate-hexane. The desired product eluted with 30% ethyl acetate-hexane and fractions containing pure product were concentrated to afford 0.503 g (60%) of title product as a light-brown solid.

Example 4

[1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one, monohydrate

a) [1S-(1α,3α,4β)]-6-(Phenylmethoxy)-9-[2-methylene-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-9H-purin-2-amine

A solution of [1S-(1α,3α,4β)]-N-[(4-methoxyphenyl)diphenylmethyl]-6-(phenylmethoxy)-9-[2-methylene-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-9H-purin-2-amine (150 mg, 0.183 mmole) [prepared as described in Example 1 (a) through (f)] in 2 ml of tetrahydrofuran and 1 ml of 1N aqueous hydrochloric acid was stirred at room temperature for 30 minutes. TLC confirmed the absence of starting material. About 5 ml of water and 2 ml of ethyl acetate were added to the reaction mixture and then the pH was raised to about 6.8 by the addition of aqueous sodium hydroxide. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried (sodium sulfate) and concentrated. The resulting crude material was chromatographed on a column (2.5 x 20 cm) of silica gel, eluting with a stepwise gradient of ethyl acetate-hexane. The product containing fractions were combined and concentrated to afford 80 mg of pure title product (80% yield) as a colorless oil which later solidified; m.p. 89 - 91°C.

b) [1S-(1α,3α,4β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one, monohydrate

To a solution of the product from part (a) (70 mg, 0.13 mmole) in dichloromethane (2 ml) at -78°C was added 1M boron trichloride (1.3 ml, 1.3 mmole) in dichloromethane dropwise over 1 minute. The turbid light-yellow reaction mixture was stirred for 2 hours at -78°C, for 40 minutes at -20°C, and for 20 minutes at 0°C. TLC showed a single lower R_f product spot. The reaction mixture was recooled to -78°C and methanol (3 ml) was added slowly affording a clear, colorless solution. This solution was warmed to room temperature, concentrated to dryness, and reconcentrated once from methanol to afford 58 mg of crude product as a light tan solid (greater than about 95% purity).

This crude product was dissolved in water and extracted with ether. The pH of the aqueous solution was adjusted to 7 with aqueous sodium hydroxide. The aqueous solution was applied to a column (2.5 x 5 cm) of HP-20 reverse phase resin and eluted with water (75 ml), 5% acetonitrile (50 ml), and 10% acetonitrile (75 ml). The product was eluted in the 5% - 10% acetonitrile fractions. The product containing fractions were combined and concentrated to afford the title product as a white powdery solid; m.p. >225°C (dec.).

TLC: R_f = 0.24; silica gel; chloroform:methanol:aqueous ammonium hydroxide 6:3:1; UV detection.

Anal. calc'd for $C_{12}H_{15}N_5O_3 \cdot 1.0\ H_2O$:

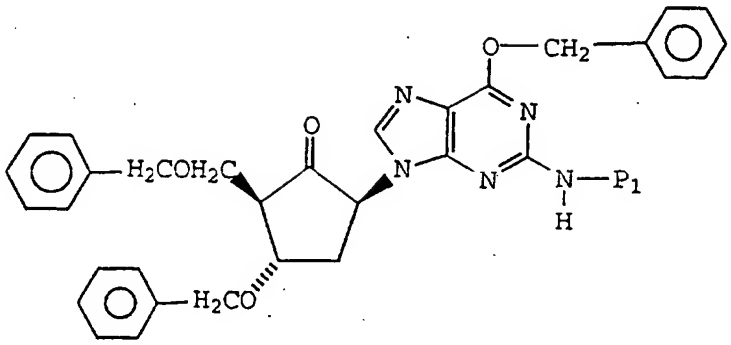
Calculated: C, 48.81; H, 5.80; N, 23.72;

Found: C, 48.70; H, 5.76; N, 23.54.

What is claimed is:

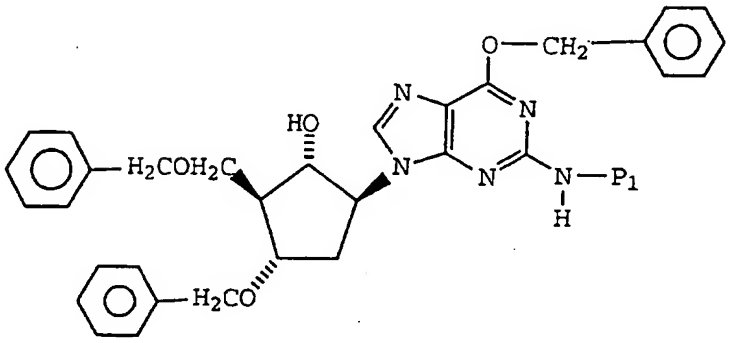
1. A process for preparing the compound of the formula

(VIII)



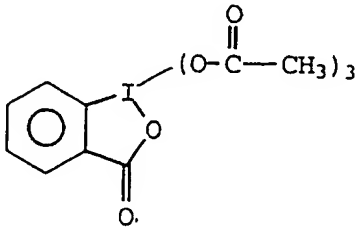
wherein P_1 is a trityl or substituted trityl protecting group which comprises oxidizing the cyclopentanol of the formula

(VI)



by reacting with the Dess-Martin periodinane of the formula

(VII)

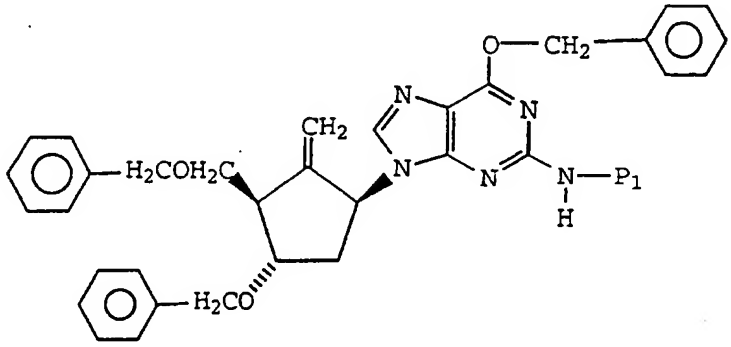


2. A process of Claim 1 wherein the cyclopentanol of formula VI is reacted with from about 1 to about 4 equivalents of the Dess-Martin periodinane of formula VII, the reaction is performed at a temperature of from about -20°C to about 40°C, the reaction is performed in a chlorinated solvent such as dichloromethane, chloroform, or 1,2-dichloroethane, or is performed in acetonitrile, and water or t-butanol can optionally be included in the reaction mixture at up to about 1 equivalent of the Dess-Martin periodinane of formula VII.

3. A process of Claim 2 wherein the cyclopentanol of formula VI is reacted with about 2 equivalents of the Dess-Martin periodinane of formula VII, the reaction is performed at about room temperature, in a solvent selected from dichloromethane, chloroform, and 1,2-dichloroethane, and t-butanol is included in the reaction mixture.

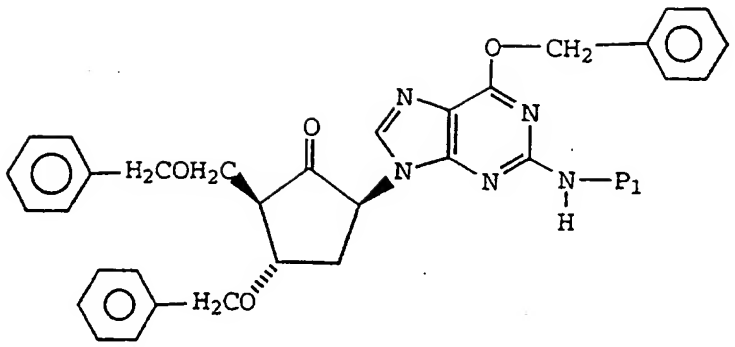
4. A process for preparing the compound of the formula

(XI)

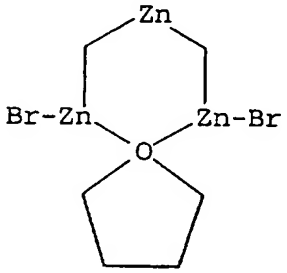


wherein P_1 is a trityl or substituted trityl protecting group which comprises methylenation of the keto compound of the formula

(VIII)

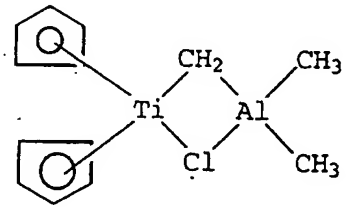


by reacting with the Nysted reagent having the formula (IX)



, or

the Tebbe reagent having the formula (X)



, or

a reagent prepared from zinc powder, diiodomethane, lead powder or lead chloride, and titanium tetrachloride in a suitable solvent.

5. A process of Claim 4 wherein the methylenation is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Nysted reagent of formula IX in a solvent such as tetrahydrofuran or hexamethylphosphoramide, the reaction mixture includes

up to 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII, and the reaction is kept at a temperature of from about -78°C to about 25°C during the initial mixing and at from about 0° to the reflux temperature of the solvent for the remainder of the reaction.

6. A process of Claim 5 wherein about 1.3 equivalents of the Nysted reagent of formula IX are employed per equivalent of the keto compound of formula VIII, about 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII is included in the reaction mixture, and the reaction is performed in tetrahydrofuran.

7. A process of Claim 4 wherein the methylenation is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Tebbe reagent of formula X in a suitable solvent such as tetrahydrofuran, and the reaction is performed at from about -78°C to about the reflux temperature of the solvent.

8. A process of Claim 7 wherein the methylenation is performed by reacting the keto compound of formula VIII with about 2 equivalents of the Tebbe reagent of formula X in tetrahydrofuran, and the reaction is performed at about 0°C during the initial mixing and at about room temperature for the remainder of the reaction.

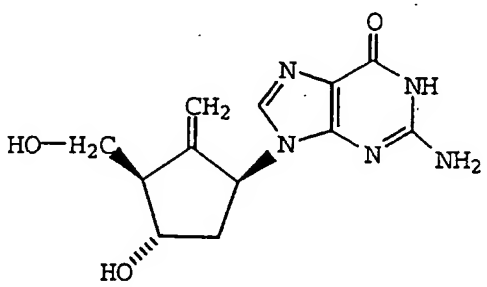
9. A process of Claim 4 wherein the methylenation is performed by reacting the keto compound of formula VIII with a reagent containing from about 2 to about 30 equivalents of zinc powder, from about 2 to about 20 equivalents of diiodomethane, from about 2 to about 4 equivalents of titanium tetrachloride, and from about 0.01 to about 1 equivalent of lead powder or lead chloride in a suitable solvent such as tetrahydrofuran, ether, or 1,2-

dimethoxyethane, and the reaction is performed at a temperature of from about -78°C to about the reflux temperature of the solvent.

10. A process of Claim 9 wherein the methylenation is performed by reacting the keto compound of formula VIII with a reagent containing from about 18 equivalents of zinc powder, about 10 equivalents of diiodomethane, about 2 equivalents of titanium tetrachloride, and about 0.09 equivalents of lead chloride in tetrahydrofuran, and the reaction is performed at about room temperature.

11. A process for preparing the compound of the formula

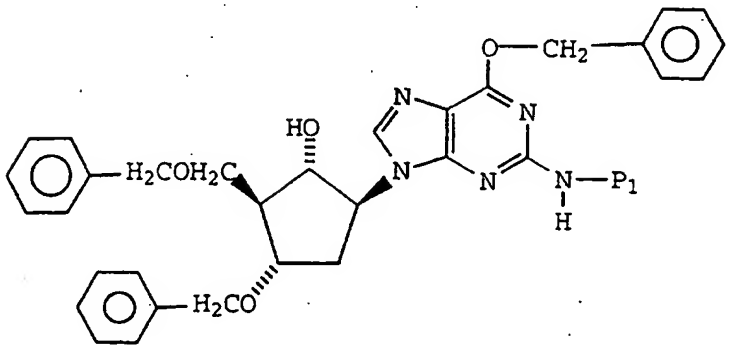
(I)



which comprises:

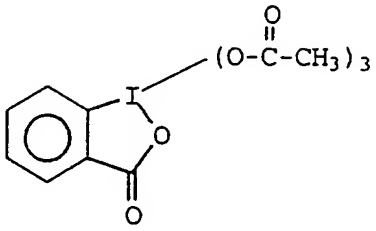
a) oxidizing the cyclopentanol of the formula

(VI)



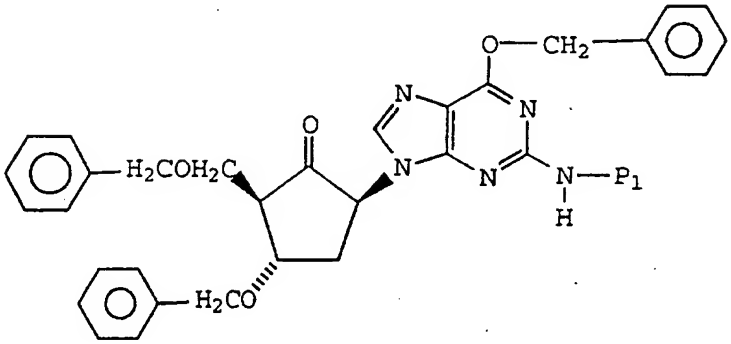
wherein P_1 is trityl or substituted trityl protecting group with the Dess-Martin periodinane of the formula

(VII)



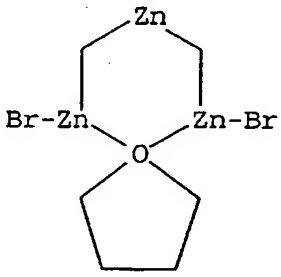
to give the keto compound of the formula

(VIII)



b) methylenation of the keto compound of formula VIII by reacting with the Nysted reagent having the formula

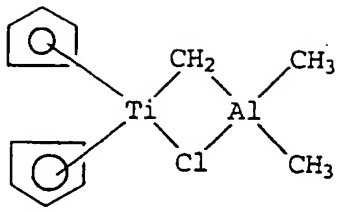
(IX)



, or

the Tebbe reagent having the formula

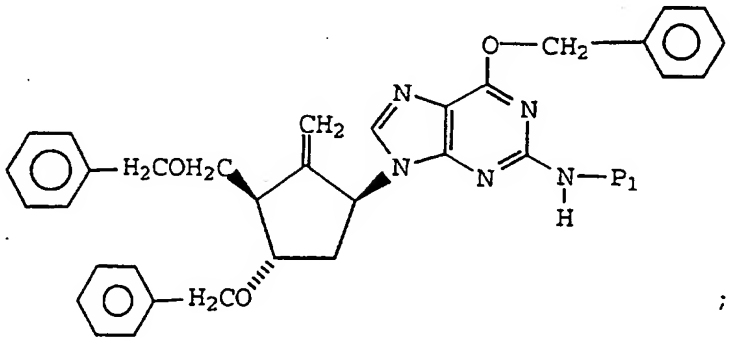
(X)



, or

a reagent prepared from zinc powder, diiodomethane, lead powder or lead chloride, and titanium tetrachloride in a suitable solvent to give the methylene compound of the formula

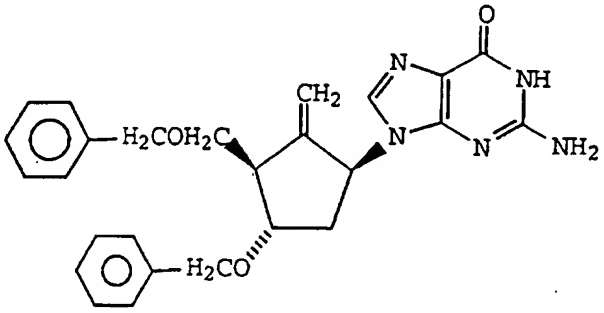
(XI)



;

c) treating the compound of formula XI with aqueous hydrochloric acid for sufficient time to remove the O-benzyl and P_1 guanine protecting groups and give the compound of the formula

(XII)



; and

d) treating the compound of formula XII with boron trichloride to remove the two benzyl protecting groups and yield the product of formula I.

12. A process of Claim 11 wherein in step (a) the cyclopentanol of formula VI is reacted with from about 1 to about 4 equivalents of the Dess-Martin periodinane of formula VII, the reaction is performed at a temperature of from about -20°C to about 40°C, the reaction is performed in a chlorinated solvent such as dichloromethane, chloroform, or 1,2-dichloroethane, or is performed in acetonitrile, and water or t-butanol can optionally be included in the reaction mixture at up to about 1 equivalent of the Dess-Martin periodinane of formula VII.

13. A process of Claim 12 wherein in step (a) the cyclopentanol of formula VI is reacted with about 2 equivalents of the Dess-Martin periodinane of formula VII, the reaction is performed at about room temperature, in a solvent selected from dichloromethane, chloroform, and 1,2-dichloroethane, and t-butanol is included in the reaction mixture.

14. A process of Claim 11 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Nysted reagent of formula IX in a solvent such as tetrahydrofuran or hexamethylphosphoramide, the reaction mixture includes up to 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII, and the reaction is kept at a temperature of from about -78°C to about 25°C during the initial mixing and at from about 0° to the reflux temperature of the solvent for the remainder of the reaction.

15. A process of Claim 14 wherein in step (b) about 1.3 equivalents of the Nysted reagent of formula IX are employed per equivalent of the keto compound of formula

VIII, about 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII is included in the reaction mixture, and the reaction is performed in tetrahydrofuran.

16. A process of Claim 11 wherein the methylanation in step (b) is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Tebbe reagent of formula X in a suitable solvent such as tetrahydrofuran, and where the reaction is performed at from about -78°C to about the reflux temperature of the solvent.

17. A process of Claim 16 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with about 2 equivalents of the Tebbe reagent of formula X in tetrahydrofuran, and the reaction is performed at about 0°C during the initial mixing and at about room temperature for the remainder of the reaction.

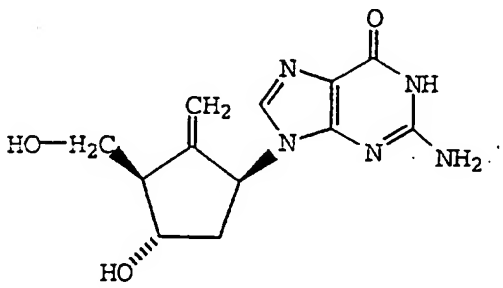
18. A process of Claim 11 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with a reagent containing from about 2 to about 30 equivalents of zinc powder, from about 2 to about 20 equivalents of diiodomethane, from about 2 to about 4 equivalents of titanium tetrachloride, and from about 0.01 to about 1 equivalent of lead powder or lead chloride in a suitable solvent such as tetrahydrofuran, ether, or 1,2-dimethoxyethane and the reaction is performed at a temperature of from about -78°C to about the reflux temperature of the solvent.

19. A process of Claim 18 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with a reagent containing from about 18 equivalents of zinc powder, about 2 equivalents of titanium tetrachloride, about 10 equivalents of diiodomethane, and

about 0.09 equivalents of lead chloride in tetrahydrofuran, and the reaction is performed at about room temperature.

20. A process for preparing the compound of the formula

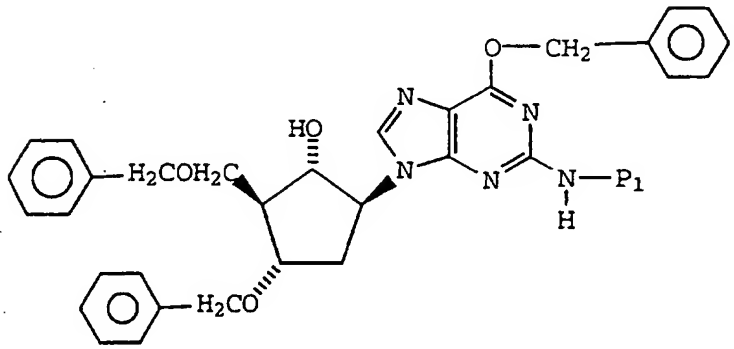
(I)



which comprises:

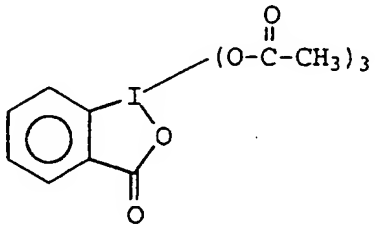
a) oxidizing the cyclopentanol of the formula

(VI)



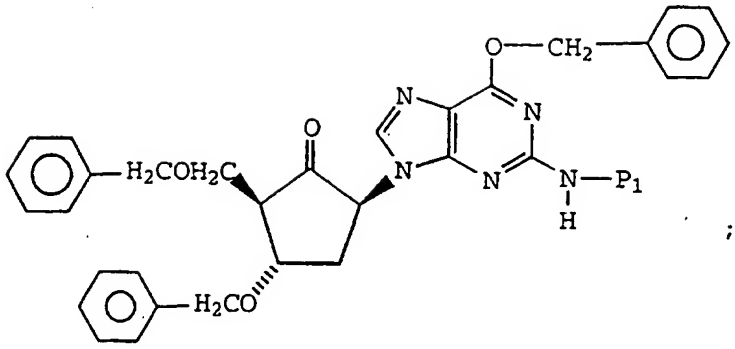
wherein P_1 is a trityl or substituted trityl protecting group with the Dess-Martin periodinane of the formula

(VII)



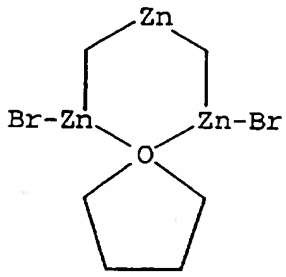
to give the keto compound of the formula

(VIII)



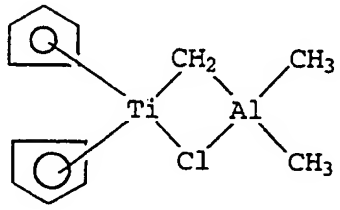
;

b) methylenation of the keto compound of formula VIII by reacting with the Nysted reagent having the formula (IX)



, or

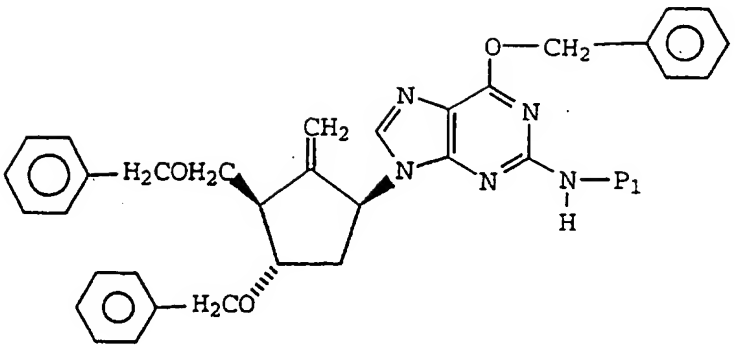
the Tebbe reagent having the formula (X)



, or

a reagent prepared from zinc powder, diiodomethane, lead powder or lead chloride, and titanium tetrachloride in a suitable solvent to give the methylene compound of the formula

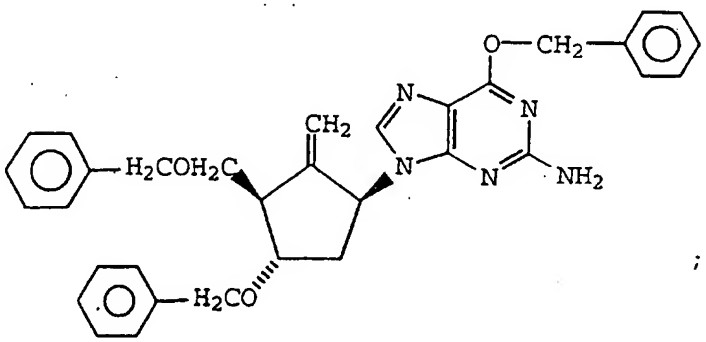
(XI)



;

c) treating the compound of formula XI with aqueous hydrochloric acid for sufficient time to remove only the P_1 protecting group and give the compound of the formula

(XIII)



; and

d) treating the compound of formula XIII with boron trichloride to remove the three benzyl protecting groups and yield the product of formula I.

21. A process of Claim 20 wherein in step (a) the cyclopentanol of formula VI is reacted with from about 1 to about 4 equivalents of the Dess-Martin periodinane of formula VII, the reaction is performed at a temperature of from about -20°C to about 40°C, the reaction is performed in chlorinated solvent such as dichloromethane, chloroform, or 1,2-dichloroethane, or is performed in acetonitrile, and where water or t-butanol can optionally be included in the

reaction mixture at up to about 1 equivalent of the Dess-Martin periodane of formula VII.

22. A process of Claim 21 wherein in step (a) the cyclopentanol of formula VI is reacted with about 2 equivalents of the Dess-Martin periodinane of formula VII, the reaction is performed at about room temperature, in a solvent selected from dichloromethane, chloroform, and 1,2-dichloroethane, and t-butanol is included in the reaction mixture.

23. A process of Claim 20 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Nysted reagent of formula IX in a solvent such as tetrahydrofuran or hexamethylphosphoramide, the reaction mixture includes up to 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII, and the reaction is kept at a temperature of from about -78°C to about 25°C during the initial mixing and at from about 0° to the reflux temperature of the solvent for the remainder of the reaction.

24. A process of Claim 23 wherein in step (b) about 1.3 equivalents of the Nysted reagent of formula IX are employed per equivalent of the keto compound of formula VIII, about 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII is included in the reaction mixture, and the reaction is performed in tetrahydrofuran.

25. A process of Claim 20 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Tebbe reagent of formula X in a suitable solvent such as tetrahydrofuran, and the reaction is performed at from about -78°C to about the reflux temperature of the solvent.

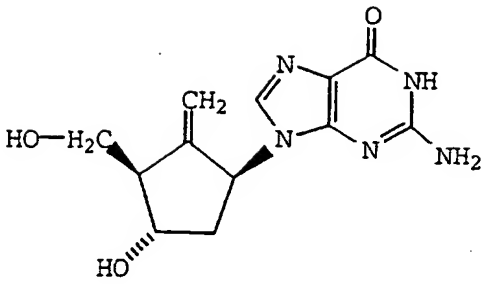
26. A process of Claim 25 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with about 2 equivalents of the Tebbe reagent of formula X in tetrahydrofuran, and the reaction is performed at about 0°C during the initial mixing and at about room temperature for the remainder of the reaction.

27. A process of Claim 20 wherein the methylenation in step (b) is performed by reacting the keto compound of formula VIII with a reagent containing from about 2 to about 30 equivalents of zinc powder, from about 2 to about 20 equivalents of diiodomethane, from about 2 to about 4 equivalents of titanium tetrachloride, and from about 0.01 to about 1 equivalent of lead powder or lead chloride in a suitable solvent such as tetrahydrofuran, ether, or 1,2-dimethoxyethane, and the reaction is performed at a temperature of from about -78°C to about the reflux temperature of the solvent.

28. A process of Claim 27 wherein the methylenation is performed by reacting the keto compound of formula VIII with a reagent containing from about 18 equivalents of zinc powder, about 10 equivalents of diiodomethane, about 2 equivalents of titanium tetrachloride, and about 0.09 equivalents of lead chloride in tetrahydrofuran, and the reaction is performed at about room temperature.

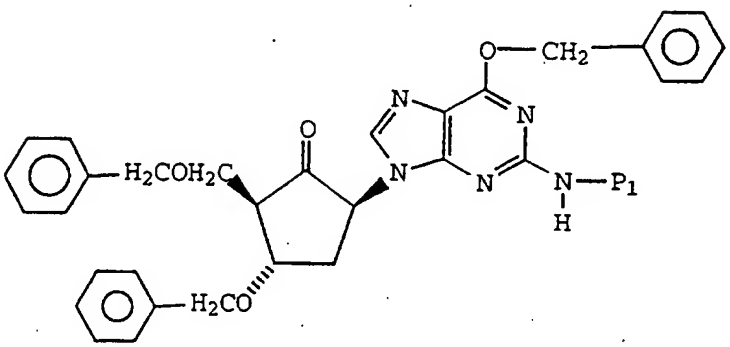
29. A process for preparing the compound of the formula

(I)



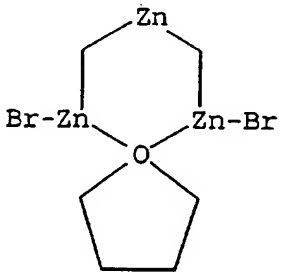
which comprises:

a) methylenation of the keto compound of formula (VIII)



by reacting with the Nysted reagent having the formula

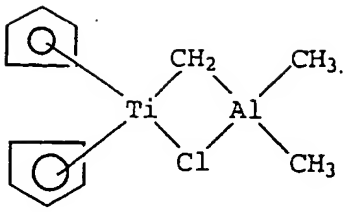
(IX)



, or

the Tebbe reagent having the formula

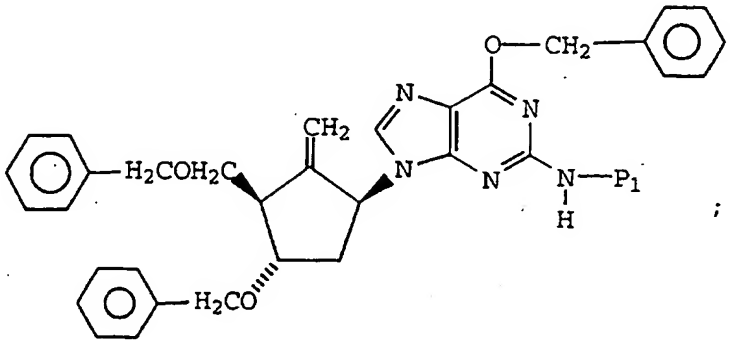
(X)



, or

a reagent prepared from zinc powder, diiodomethane, lead powder or lead chloride, and titanium tetrachloride in a suitable solvent to give the methylene compound of the formula

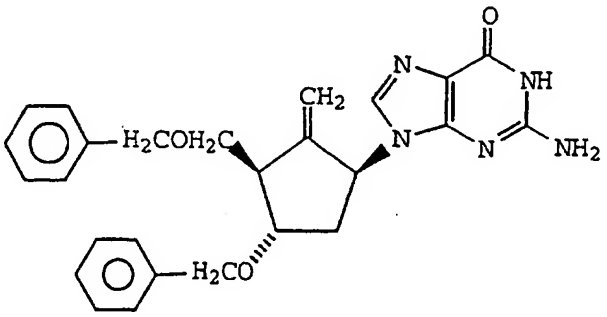
(XI)



;

b) treating the compound of formula XI with aqueous hydrochloric acid for sufficient time to remove the O-benzyl and P_1 guanine protecting groups and give the compound of the formula

(XII)



; and

c) treating the compound of formula XII with boron trichloride to remove the two benzyl protecting groups and yield the product of formula I.

30. A process of Claim 29 wherein in step (a) the methylenation is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Nysted reagent of formula IX in a solvent such as tetrahydrofuran or hexamethylphosphoramide, the reaction mixture includes up to 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII, and the reaction is kept at a temperature of from about -78°C to about 25°C during the initial mixing and at from about 0° to the reflux temperature of the solvent for the remainder of the reaction.

31. A process of Claim 30 wherein in step (a) about 1.3 equivalents of the Nysted reagent of formula IX are employed per equivalent of the keto compound of formula VIII, about 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII is included in the reaction mixture, and the reaction is performed in tetrahydrofuran.

32. A process of Claim 29 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Tebbe reagent of formula X in a suitable solvent such as tetrahydrofuran, and the reaction is performed at from about -78°C to about the reflux temperature of the solvent.

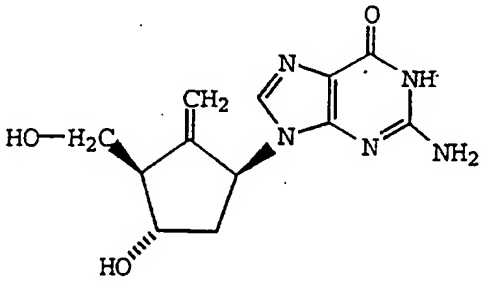
33. A process of Claim 32 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with about 2 equivalents of the Tebbe reagent of formula X in tetrahydrofuran, and the reaction is performed at about 0°C during the initial mixing and at about room temperature for the remainder of the reaction.

34. A process of Claim 29 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with a reagent containing from about 2 to about 30 equivalents of zinc powder, from about 2 to about 20 equivalents of diiodomethane, from about 2 to about 4 equivalents of titanium tetrachloride, and from about 0.01 to about 1 equivalent of lead powder or lead chloride in a suitable solvent such as tetrahydrofuran, ether, or 1,2-dimethoxyethane, and the reaction is performed at a temperature of from about -78°C to about the reflux temperature of the solvent.

35. A process of Claim 34 wherein the methylenation is performed by reacting the keto compound of formula VIII with a reagent containing from about 18 equivalents of zinc powder, about 10 equivalents of diiodomethane, about 2 equivalents of titanium tetrachloride, and about 0.09 equivalents of lead chloride in tetrahydrofuran, and the reaction is performed at about room temperature.

36. A process for preparing the compound of the formula

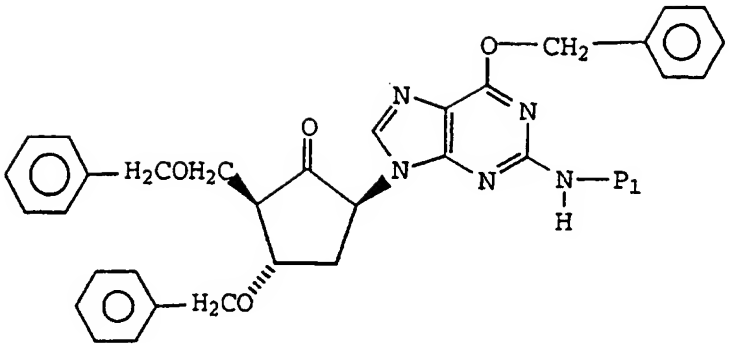
(I)



which comprises:

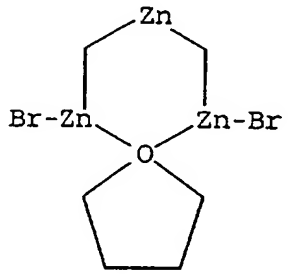
a) methylenation of the keto compound of the formula

(VIII)



by reacting with the Nysted reagent having the formula

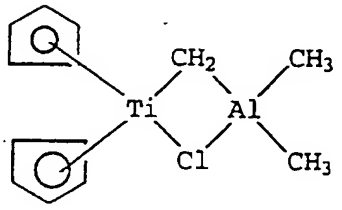
(IX)



, or

the Tebbe reagent having the formula

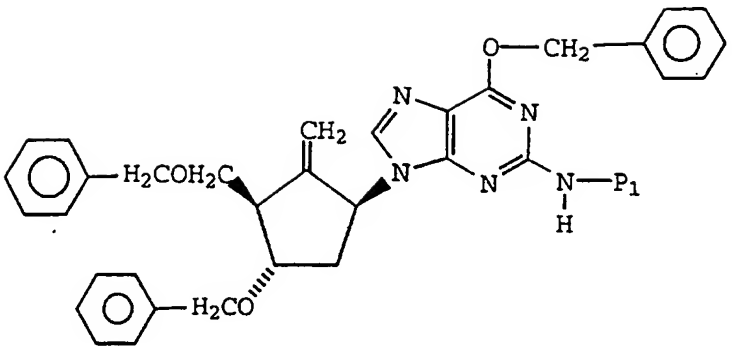
(X)



, or

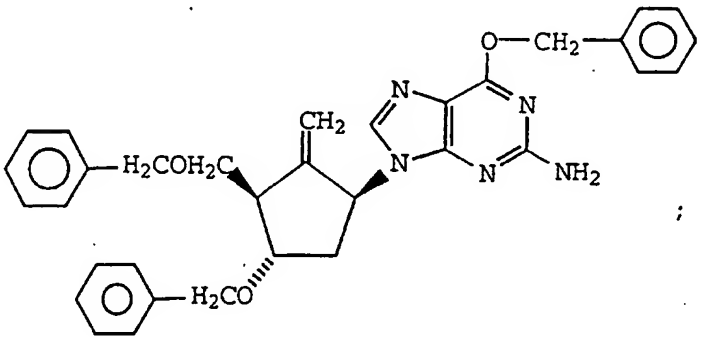
a reagent prepared from zinc powder, diiodomethane, lead powder or lead chloride, and titanium tetrachloride in a suitable solvent to give the methylene compound of the formula

(XI)



;

b) treating the compound of formula XI with aqueous hydrochloric acid for sufficient time to remove only the P_1 protecting group and give the compound of the formula (XIII)



; and

c) treating the compound of formula XIII with boron trichloride to remove the three benzyl protecting groups and yield the product of formula I.

37. A process of Claim 36 wherein in step (a) the methylenation is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Nysted reagent of formula IX in a solvent such as tetrahydrofuran or hexamethylphosphoramide, the reaction mixture includes up to 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII, and the reaction is kept at a temperature of from about -78°C to about 25°C during the initial mixing

and at from about 0° to the reflux temperature of the solvent for the remainder of the reaction.

38. A process of Claim 37 wherein in step (a) about 1.3 equivalents of the Nysted reagent of formula IX are employed per equivalent of the keto compound of formula VIII, about 1 equivalent of titanium tetrachloride per equivalent of the keto compound of formula VIII is included in the reaction mixture, and the reaction is performed in tetrahydrofuran.

39. A process of Claim 36 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with from about 1 to about 4 equivalents of the Tebbe reagent of formula X in a suitable solvent such as tetrahydrofuran, and the reaction is performed at from about -78°C to about the reflux temperature of the solvent.

40. A process of Claim 39 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with about 2 equivalents of the Tebbe reagent of formula X in tetrahydrofuran, and the reaction is performed at about 0°C during the initial mixing and at about room temperature for the remainder of the reaction.

41. A process of Claim 36 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with a reagent containing from about 2 to about 30 equivalents of zinc powder, from about 2 to about 20 equivalents of diiodomethane, from about 2 to about 4 equivalents of titanium tetrachloride, and from about 0.01 to about 1 equivalent of lead powder or lead chloride in a suitable solvent such as tetrahydrofuran, ether, or 1,2-dimethoxyethane and the reaction is performed at a temperature of from about -78°C to about the reflux temperature of the solvent.

42. A process of Claim 41 wherein the methylenation in step (a) is performed by reacting the keto compound of formula VIII with a reagent containing from about 18 equivalents of zinc powder, about 10 equivalents of diiodomethane, about 2 equivalents of titanium tetrachloride, and about 0.09 equivalents of lead chloride in tetrahydrofuran, and the reaction is performed at about room temperature.

INTERNATIONAL SEARCH REPORT

Inter onal application No.
PCT/US97/15007

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 473/18
US CL :544/276
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/276

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y -- A	US 5,206,244 A (E.R. ZAHLER et al.) 27 April 1993, columns 5-6.	1-26, 29-33, 36-40 --- 27, 28, 34, 35, 41, 42
Y -- A	ROBINS et al. Periodinane Oxidation, Selective Primary Deprotection and Remarkably Stereoselective Reduction of *tert*-Butyldimethylsilyl-Protected Ribonucleosides. Synthesis of 9-(β-D-Xylofuranosyl)adenine or 3'-Deuterioadenosine from Adenosine. Journal of Organic Chemistry. 1990, Vol. 55, pages 410-412, especially Scheme 1, first step.	1-28 --- 29-42

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 18 OCTOBER 1997	Date of mailing of the international search report 04 DEC 1997
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15007

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y -- A	A. SPEICHER et al. Dess-Martin-Periodinan (DMP) J. Prakt. Chem. July 1996, Vol. 338, pages 588-590, especially page 589, 10 to 11.	1-28 ------- 29-42
Y -- A	US 3,865,848 A (L.N. NYSTED) 11 February 1975, Examples 4-20.	1-26, 29-31, 36-38 ------- 27, 28, 32-35, 39-42
Y -- X	PINE et al. Ketone Methylenation Using the Tebbe and Wittig Reagents - A comparison. Synthesis. February 1991, pages 165-167, especially Table, first 3 runs.	1-29, 32, 33, 36, 39, 40 ------- 30, 31, 34, 35, 37, 38, 41, 42
Y -- A	C. LAMBERTH. Tebbe's Reagent: $Cp_2TiCH_2AlClMe_2$. J. Prakt. Chem. July 1994, Vol. 336, pages 632-633, especially Formulas 9 to 10, 11 to 12 and 13 to 14.	1-29, 32, 33, 36, 39, 40 ------- 30, 31, 34, 35, 37, 38, 41, 42
Y -- A	PINE et al. Carbonyl Methylenation Using a Titanium-Aluminum (Tebbe) Complex. J. Org. Chem. 1985, Vol. 50, No. 8, pages 1212-1216, especially Formulas 20 to 21, 22 to 23 and 28-29.	1-29, 32, 33, 36, 39, 40 -------- 30, 31, 34, 35, 37, 38, 41, 42